Autosomal Dominant Tubulointerstitial Kidney Disease: Clinical Presentation of Patients With ADTKD-*UMOD* and ADTKD-*MUC1*

Nadia Ayasreh, Gemma Bullich, Rosa Miquel, Mónica Furlano, Patricia Ruiz, Laura Lorente, Oliver Valero, Miguel Angel García-González, Nisrine Arhda, Intza Garin, Víctor Martínez, Vanessa Pérez-Gómez, Xavier Fulladosa, David Arroyo, Alberto Martínez-Vea, Mario Espinosa, Jose Ballarín, Elisabet Ars, and Roser Torra**

Rationale & Objective: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a rare underdiagnosed cause of end-stage renal disease (ESRD). ADTKD is caused by mutations in at least 4 different genes: *MUC1*, *UMOD*, *HNF1B*, and *REN*.

Study Design: Retrospective cohort study.

Setting & Participants: 56 families (131 affected individuals) with ADTKD referred from different Spanish hospitals. Clinical, laboratory, radiologic, and pathologic data were collected, and genetic testing for *UMOD*, *MUC1*, *REN*, and *HNF1B* was performed.

Predictors: Hyperuricemia, ultrasound findings, renal histology, genetic mutations.

Outcomes: Age at ESRD, rate of decline in estimated glomerular filtration rate.

Results: ADTKD was diagnosed in 25 families (45%), 9 carried *UMOD* pathogenic variants (41 affected members), and 16 carried the *MUC1* pathogenic mutation c.(428)dupC (90 affected members). No pathogenic variants were identified in *REN* or *HNF1B*. Among the 77 individuals who developed ESRD, median age at onset of ESRD was 51 years for those with ADTKD-*MUC1* versus 56 years ($P = 0.1$) for those with ADTKD-*UMOD*. Individuals with the *MUC1* duplication presented higher risk for developing ESRD (HR, 2.24; $P = 0.03$). The slope of decline in estimated glomerular filtration rate showed no significant difference between groups (−3.0 mL/min/1.73 m^2 per year in the ADTKD-*UMOD* group versus −3.9 mL/min/1.73 m^2 per year in the ADTKD-*MUC1* group; $P = 0.2$). The prevalence of hyperuricemia was significantly higher in individuals with ADTKD-*UMOD* (87% vs 54%; $P = 0.006$). Although gout occurred more frequently in this group, the difference was not statistically significant (24% vs 7%; $P = 0.07$).

Limitations: Relatively small Spanish cohort. *MUC1* analysis limited to cytosine duplication.

Conclusions: The main genetic cause of ADTKD in our Spanish cohort is the *MUC1* pathogenic mutation c.(428)dupC. Renal survival may be worse in individuals with the *MUC1* mutation than in those with *UMOD* mutations. Clinical presentation does not permit distinguishing between these variants. However, hyperuricemia and gout are more frequent in individuals with ADTKD-*UMOD*.

Complete author and article information provided before references.

Correspondence to R. Torra (rtorra@fundacio-puigvert.es)

**E.A. and R.T. equally contributed to this work.*

Am J Kidney Dis. XX(XX): 1-8. Published online Month X, 2018.

doi: 10.1053/j.ajkd.2018.03.019

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a rare, but underdiagnosed, cause of end-stage renal disease (ESRD).[1] Disparities in nomenclature, the subtle phenotype of ADTKD with unspecific symptoms and slow progression, and the wide variability in age at onset of ESRD among and within families have made the diagnosis challenging.[2] In 2014, KDIGO (Kidney Disease: Improving Global Outcomes) proposed the adoption of a new terminology for this group of diseases in which the term "ADTKD" is appended by a gene-based subclassification and also suggested diagnostic criteria.[3] These diseases are clinically similar but are caused by mutations in at least 4 different genes: *MUC1*, *UMOD*, *HNF1B*, and *REN*. Recently, a new gene, *SEC61A1* (encoding protein transport protein Sec61 subunit α), has been identified in 2 families,[4] but further studies are needed to identify the pathogenicity of mutations in this gene. Recently, an association between sequence variants in mitochondrial DNA and maternally inherited interstitial kidney disease has been reported.[5]

There are some unifying characteristics of ADTKD, such as slow progressive loss of kidney function, bland urinary sediment, absent or mildly increased albuminuria, lack of severe hypertension during the early stages, normal or small kidneys on ultrasound, and renal histology showing interstitial fibrosis with tubular atrophy.[2,3] There is no evidence to establish the prevalence of the different types of ADTKD, but ADTKD-*UMOD* and ADTKD-*MUC1* are the most frequently identified forms.[3]

ADTKD-*UMOD* is caused by pathogenic variants in the *UMOD* gene, which encodes uromodulin, the most abundant protein in human urine.[6] It has previously been named medullary cystic kidney disease type II (MCKD2; OMIM [Online Mendelian Inheritance in Man] 603860), familial juvenile hyperuricemic nephropathy (FJHN; OMIM 162000), and uromodulin-associated kidney disease (UAKD).[7-11] The role that uromodulin plays in renal physiology has been widely discussed in the literature. Although identification of all its functions remains a

challenge,[12,13] some known functions are protection against urinary tract infections, prevention of urolithiasis, ensuring water impermeability, and creating the countercurrent gradient.[9,12-14] The role of uromodulin as a biomarker of chronic kidney disease (CKD) is also well known.[15]

ADTKD-*MUC1* is caused by a mutation in the *MUC1* gene (OMIM 158340; 1q22). The disease was first described in 1944 as medullary cystic kidney disease (MCKD) type I (MCKD1; OMIM 174000),[16] and years later linkage to chromosome 1q21 locus was demonstrated.[17-19] In 2012, Kirby et al[20] identified an unusual mutation in the *MUC1* gene. *MUC1* contains a GC-rich coding variable-number tandem repeat (VNTR) sequence, consisting of up to or more than 100 repeating stretches of 60 base pairs. The duplication of a single cytosine in one of the repeats was predicted to give rise to an abnormal mucin 1 protein, a transmembrane protein. Because of its location, this cytosine duplication was difficult to identify, requiring cloning, capillary sequencing, and de novo assembly of this sequence region markedly under-represented in massively parallel sequencing data.[20] This anomalous mucin 1 causes ADTKD and has been reported in 28 families with no extrarenal phenotype.[2,21,22] Recently, a novel *MUC1* mutation has been reported to segregate with ADTKD in a 15-member family. This novel mutation consists of a 2–base pair (adenine and guanine) deletion before the VNTR, which was predicted to result in a very similar protein sequence and 3-dimensional structure as the protein resulting from the cytosine duplication. Mutant MUC1 proteins are predicted to be trapped in the cytoplasm and self-aggregate.[23]

Mutations in the other genes have been described in few families. Mutations in the *REN* gene (which encodes renin) have been identified in only 14 families.[24-26] Mutations in the *HNF1B* gene (encoding hepatocyte nuclear factor 1β) have a wide range of phenotypes, but families with only kidney damage causing ADTKD are few.[27-31]

The main objectives of this study were to identify the prevalence of the different types of ADTKD in a Spanish cohort and compare the clinical characteristics depending on the causative gene.

Methods

Patients

A total of 56 families (Fig S1) referred from different Spanish hospitals were studied. We collected clinical, laboratory, radiologic, and pathologic data and performed genetic testing for *UMOD*, *MUC1*, *REN*, and *HNF1B* mutations. The study was approved by the institutional review board (2015/05c, date March 17, 2015), and all participants gave their informed consent.

Only families with autosomal dominant inheritance were included. Affected members should have kidney failure without or with minimal hematuria, absent or minimal proteinuria (protein excretion < 1 g/d) in the absence of CKD stage 3, 4, or 5. Exclusion of other causes of chronic tubulointerstitial nephropathy, such as pharmacologic or urologic causes, was mandatory.

All clinical data were recorded in a database (available on request), including sex, date of birth, age at diagnosis of kidney disease, hyperuricemia (defined as uric acid > 6 mg/dL for women and >7.05 mg/dL for men), gout, ESRD, historical kidney function, and age at last follow-up. Rate of decline in estimated glomerular filtration rate (eGFR) was analyzed using GFR estimated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation[32] in individuals with at least 3 estimated values 3 years apart. ESRD was defined as eGFR < 10 mL/min/1.73 m^2, initiation of dialysis therapy, kidney transplantation, or death from kidney failure in the absence of renal replacement therapy initiation. Age at onset of hyperuricemia was defined as the age at first diagnosis of high serum uric acid level, and age at onset of gout was defined as the patient's age at the first episode of gout arthritis. Other clinical data analyzed were the presence of hypertension, polyuria, polydipsia, proteinuria, and microhematuria. Available data from deceased family members were also collected.

Mutational Analysis

Genomic DNA was isolated from peripheral blood using the salting-out method. Mutation analysis was performed by direct sequencing of the 10 *UMOD* (GenBank accession numbers of reference sequences: NM_001008389.2 and NP_001008390.1) coding exons, exon 1 of *REN* (NM_000537.3 and NP_000528.1), and all coding exons of *HNF1B* (NM_000458.3, NP_000449.1), using exon-flanking primers (sequences available on request). *HNF1B* deletion/duplication screening was performed using quantitative multiplex polymerase chain reaction of short fluorescent fragments.[33] The cytosine duplication in the VNTR of *MUC1* [NM_001204286.1:c.(428)dupC; NC_000001.10:g.(155161732)dupG] was screened using SNaPshot (ThermoFisher Scientific) minisequencing, as previously described.[2] The technique was validated by analysis of 17 samples at the Broad Institute (Cambridge, MA) with acquisition of identical results.

Missense variants were evaluated by taking into consideration the evolutionary conservation of the amino acid residue in orthologs, population data,[34,35] and 3 computational predictors.[36-38] Missense variants altering highly conserved amino acids among orthologs, not reported in the population databases or reported with allele frequency < 0.0001 and predicted to be deleterious by most computational prediction methods used, were classified as likely pathogenic variants and considered to be disease-causing mutations. Segregation of the detected variants with the disease was assessed for all available family members.